MENTAL HEALTH

The Nikean Psychedelic Psychotherapy Research Centre

UHN Centre for Mental Health

Psilocybin-assisted psychotherapy: clinical research

7 May 2022

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  - **Leonard Latchman and Amanda Petrovic Psychedelic Therapy Education Fund**
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  - Nil

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FACULTY/PRESENTER DISCLOSURE

- Faculty: Daniel Rosenbaum, MD, FRCPC
- Relationships with financial sponsors:
  - Nikean Foundation

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Learning Objectives

By the end of the presentation, participants will be able to:

1. Describe important safety considerations around psilocybin, including potential adverse effects, contraindications, and drug-drug interactions

2. Discuss key findings from contemporary clinical trials of psilocybin-assisted psychotherapy for the treatment of depression, cancer-associated distress, and substance use disorders

3. Apply knowledge to patient care

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Outline

1. Safety, contraindications, drug-drug interactions
2. Therapeutic mechanisms
3. Depression & TRD
4. Palliative & cancer care
5. Substance use disorders
6. Methodological limitations & other considerations
7. Legality / regulatory environment

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NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site | PRS Login

Home > Search Results

Modify Search | Start Over

70 Studies found for: **psilocybin** | **Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies**

Applied Filters: ☑ **Recruiting** ☑ **Not yet recruiting** ☑ **Active not recruiting** ☑ **Enrolling by invitation**

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Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine)

- Naturally-occurring compound produced by ~200 species of fungi
- Active metabolite: *psilocin*
- Broad range of dosing
- Duration and quality of drug experience variable
  - Subjective effects usually begin 20-40 min after ingestion
  - Peak after 60-90 min
  - Total duration ~6 hours
- Essential importance of context
  - Set & setting
- Physiologic effects:
  - Mild increases in BP and HR (transient, dose-dependent)
  - Headache, nausea, dizziness, fatigue

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Safety – psilocybin

- Wide margin of safety
  - Lethal doses estimated >1000-fold higher than therapeutic doses
- Contraindications:
  - Medical
    - Uncontrolled hypertension
    - Recent stroke or MI
    - Arrhythmias
    - CNS disease (mets, seizures)
    - Insulin-dependent diabetes
  - Psychiatric
    - Bipolar I or II disorder (personal or family hx)
    - Psychosis (personal or family hx)
    - Other severe disorders

Original Papers

Psychopharm

Human hallucinogen research: guidelines for safety

MW Johnson *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, School of Medicine, Baltimore, MD, USA.*
WA Richards *Johns Hopkins Bayview Medical Center, Baltimore, MD, USA.*
RR Griffiths *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; Department of Neuroscience, Johns Hopkins University, School of Medicine, Baltimore, MD, USA.*

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https://doi.org/10.1007/s00213-022-06083-y

REVIEW

Drug-drug interactions between psychiatric medications and MDMA or psilocybin: a systematic review

Aryan Sarparast[1] · Kelan Thomas[2] · Benjamin Malcolm[3] · Christopher S. Stauffer[1,4]

Received: 4 October 2021 / Accepted: 3 February 2022

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Safety – cont'd

- Pharmacokinetics → ALP, **MAO-A**, UGTIA10
  - Because minimal MAO reuptake inhibition (i.e., no SERT activity), serotonin toxicity unlikely
  - Drug-drug interactions & psychotropic meds:
    - Antidepressants
    - Antipsychotics
    - Mood stabilizers → lithium
- Persisting adverse effects rare
  - HPPD
  - Addiction
  - Psychosis vs. "spiritual emergency"
  - No driving on session day
- "Behavioural toxicity" & psychological risks

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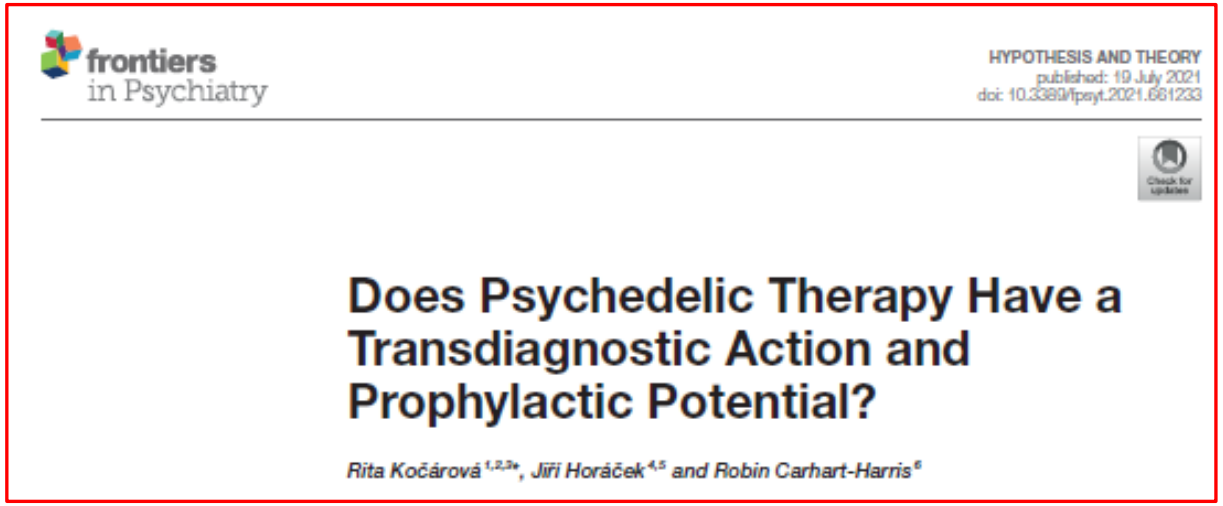
Therapeutic Mechanisms

- Neurobiological
  - ↑ neuronal plasticity
    - *"**Psychoplastogens**"*
- Psychological
  - ↑ psychological flexibility
  - ↑ mindfulness
- Experiential
  - NOSCs
  - Emotional breakthrough
  - Psychological insight
- Spiritual



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DEPRESSION

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Non-pharma-sponsored trials

1. **Carhart-Harris et al. (2016/2018)**
   - Open-label feasibility study, TRD, n=12/20, 🍄🍄, 6-mo f/u
     - No SAEs
     - Significant reduction in depressive symptoms, associated w/ ratings of acute experience

2. **Davis et al. (2021)**
   - RCT (waitlist control), MDD, n=24, 🍄🍄, 4-week f/u
     - Large effect size & high rates or response and remission
   - Guskayan et al (2022) – 12-month f/u → sustained sig. depression scores, response & remission rates

3. **Carhart-Harris et al. (2021)**
   - RCT (psilocybin vs. escitalopram – "double dummy"), MDD, n=59, 🍄🍄, 6/week f/u
     - On primary outcome (QIDS), no sig diff btw groups
     - Overall rates of AEs similar, but anxiety, dry mouth, sexual dysfunction, flat affect in SSRI group only

Qualitative research

1. Watts et al. (2017)
   - ICL open-label trial, thematic analysis of participant reports (n=20)
   - **Connectedness**
     - With self, others, the world, and all of humanity
     - Formulation: depression ↔ disconnection

2. Davis et al. (2021)
   - JHU waitlist control RCT
   - **Emotional release and resolution**
   - Peace, acceptance, letting go (of pain, sadness, trauma)

Pharma: Compass Pathways COMP360

**Caveat: “topline results” = press-release only (i.e., no peer-reviewed publications)

Design: Phase IIb, DB-RCT, placebo-controlled, n=233 (multi-site), TRD, 🍄 (1mg vs. 10mg vs. 25mg)

- Psychological support unclear

Preliminary efficacy: rapid, significant reductions in depression scores

- “Positive” findings at 3-week mark

Safety: **12 SAEs (incl. suicidal behaviour, self-injury, and SI) – more frequent in 25mg group than the 10mg or 1mg groups

Stock price fell

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CANCER

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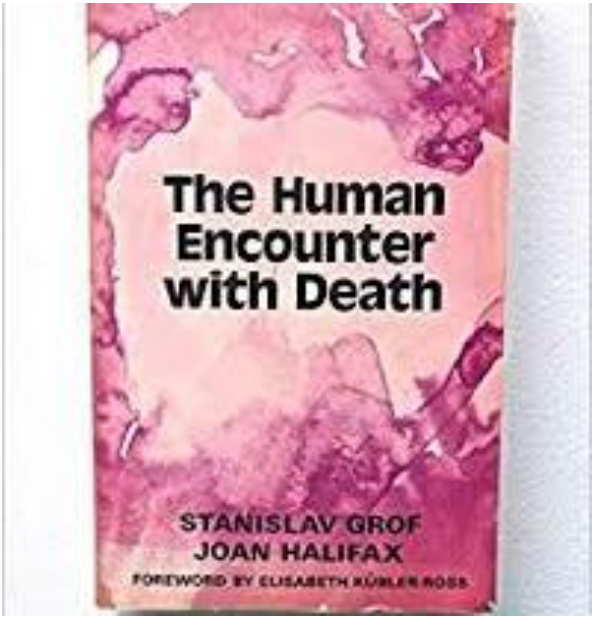
Psychedelic-Assisted Psychotherapy for Existential/End-of-Life Distress

Between 1964 and 1980:

- 6 open label trials
- Total n=341 participants, with vast majority having advanced or terminal cancer diagnoses



Between 2011 and 2016:

- 4 RCTs
- 3 psilocybin RCTs (all American) modelled after the Spring Grove program developed by Grof et al.
- Total n=92 patients
- **Rapid, robust, and sustained improvements** in cancer-related psychological and existential distress

Safety

- No SAEs (medical or psychological) in contemporary clinical trials in cancer patients
- Common AEs:
  - Transient, dose-dependent, non-clinically significant ↑HR and BP
  - Headache
  - Nausea
  - Psychological discomfort / anxiety

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Article

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2017, Vol. 57(5) 488–519

DOI: 10.1177/0022167817715966
journals.sagepub.com/home/jhp
SAGE

Cancer at the Dinner Table: Experiences of Psilocybin-Assisted Psychotherapy for the Treatment of Cancer-Related Distress

Thomas C. Swift[1], Alexander B. Belser[2], Gabrielle Agin-Liebes[3], Neşe Devenot[4], Sara Terrana[5], Harris L. Friedman[6,7], Jeffrey Guss[2,8], Anthony P. Bossis[2,8], and Stephen Ross[2,8]

10 Themes

- Anxiety & trauma related to cancer
- Perceived lack of available emotional support
- **Immersive and distressing effects of the psilocybin session**
- **Reconciliations with death**
- **Acknowledgement of cancer's place in life**
- **Emotional uncoupling from cancer**
- **Spiritual or religious interpretations of the experience**
- **Reconnection to life**
- **Reclaiming of presence**
- **Greater confidence in the face of cancer recurrence**

SUBSTANCE USE DISORDERS

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Table 1
Classic Psychedelic Studies in SUD Treatment.

Thomas et al., 2013	Hendricks et al., (2018b)	Savage & McCabe, 1973	Garcia-Romeu et al., 2014	Johnson et al., 2014; Johnson, Garcia-Romeu, & Griffiths, 2017	Bogenschutz et al., 2015	Krebs & Johansen, 2012	Study
Various	Cocaine	Heroin	Tobacco	Tobacco	Alcohol	Alcohol	Drug of Addiction
Ayahuasca	Psilocybin	LSD	Psilocybin	Psilocybin	Psilocybin	LSD	Classic Psychedelic
Observational study	Randomized controlled clinical trial [ongoing]	Randomized controlled clinical trial	Secondary analysis	Open-label	Open-label	Meta-analysis of randomized control trials	Method
12	10 (expected 40)	78	15	15	10	536	N=
Self-reported alcohol, tobacco, and cocaine use declined, but that of cannabis and opiates did not.	The psilocybin group reported significantly fewer days of cocaine use compared to those receiving diphenhydramine, significant through the 6 month follow up	At the 12-month follow up, 25% of LSD participants were abstinent, as compared to 5% of controls	Smoking cessation outcomes were correlated with mystical experience ratings.	12 out of 15 participants (80%) showed abstinence at 6-month follow up. Long-term follow up found 67% to be abstinent at 12 months and 60% at ≥16 months	Increased abstinence, with both drinking and heavy drinking days significantly reduced.	Significant larger decline in alcohol misuse for LSD patients (59% vs. 38%).	Outcomes

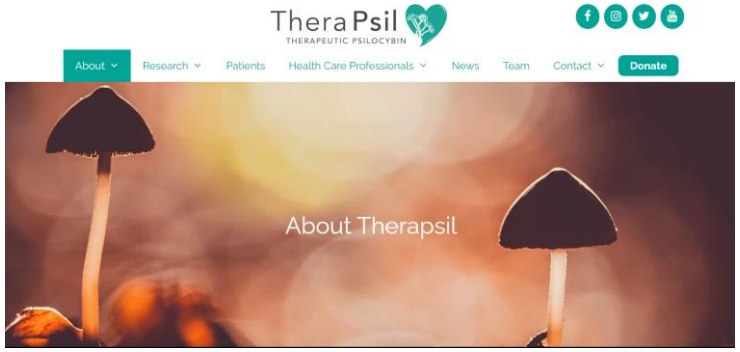
from Yaden et al. (2021)

JOHNS HOPKINS RECEIVES FIRST FEDERAL GRANT FOR PSYCHEDELIC TREATMENT RESEARCH IN 50 YEARS

The nearly $4M NIH grant will fund a multisite study of the effects of 'magic mushrooms' and talk therapy on quitting smoking

Marisol Martinez / Oct 20, 2021

Regulatory Environment



- Psilocybin (& all classic psychedelics) are Schedule III substances under the *CDSA*
  - Also restricted drugs under Part J of *Food and Drug Regulations*

- **Section 56 Exemptions**
- **Special Access Program**

- Psilocybin-assisted psychotherapy for TRD/MDD → FDA approval 2025?
- Future?
  - Regulation
  - Licensed clinics
  - License to use

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Special Access Program (SAP) for Drugs

Taken from Health Canada presentation

- Health Canada may authorize the sale of a non-marketed drug for emergency treatment of an individual patient
- Requirements:
  - The patient suffers from a serious or life-threatening condition
  - Conventional therapies have been tried and failed, considered but deemed unsuitable, or are unavailable in Canada
  - There is sufficient data to support the requested use

Limitations & challenges – psilocybin research

- Simply not yet enough research
- Existing research has major shortcomings
  - Blinding challenges
  - Expectancy confound
  - Short f/u periods
- Conflicts of interest
- External validity
  - Highly motivated patients
  - Previous psychedelic experiences
  - Diversity issues

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Expectations: hope vs. hype

Furthermore, **psilocybin therapy is not a panacea**, human suffering is not a simple problem, and depression is a dynamic, heterogenous process. Even if psilocybin therapy garners regulatory approval in the coming years, it **will not dissolve the structures and determinants that create an environment wherein a diathesis for depression is fostered**. Whether the effects of psilocybin therapy will meet the **impossibly high expectations** it is garnering in the public is also yet to be determined. Nevertheless, because psilocybin therapy offers a disruptive pharmacological approach that threatens our current understanding of the chronic and debilitating lifetime course of depression, there is **hope** that it may offer an alternative effective treatment option for those in desperate need of relief.

- Agin-Liebes & Davis (2021)

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Thank you!

Wisdom of the Universe
- Christi Belcourt